REMARKS

Claims 81, 93, 106, and 176-243 are pending. Claims 81, 93, 106, 176, 182, 194, 204, 214, 225, and 234 have been amended for consistency and to more clearly describe the claimed invention. Basis for amended claims 81, 93, 106, 176, 182, 194, 204, 214, 225, and 234 can be found throughout the specification as originally filed, for example, at pages 92-93. Thus, the claims are fully supported by the specification as filed and no new matter is added. Entry of the amendments is respectfully requested.

Regarding 35 U.S.C. § 101

Claims 81, 93, 106, and 176-243 stand rejected under 35 U.S.C. § 101 allegedly "because the claimed invention is not supported by either a specific asserted utility or a well established utility." Office Action mailed February 21, 2007 (Office Action), at page 2. Applicants respectfully traverse.

The Examination Guidelines for the Utility Requirement (Utility Guidelines) set forth the following standard, when considering utility:

> (a) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a ''specific and substantial utility'') and the assertion would be considered credible by a person of ordinary skill in the art, **do not impose a rejection based on lack of utility.**
>
> > (1) A claimed invention must have a specific and substantial utility. This requirement excludes ''throw-away,'' ''insubstantial,'' or ''nonspecific'' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101.
> >
> > (2) Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) (emphasis added).

The specification provides a number of credible assertions of specific and substantial utility. Any one such assertion is sufficient to satisfy the utility requirement of § 101. For example:

> This invention is directed to the synthesis and use of oligomeric compounds, including oligoribonucleotides and oligoribonucleosides, useful for strand cleavage of target RNA strands.
>
> Page 1, lines 7-10.
>
> Thus the compounds of the invention can be used to modulate the expression of any suitable target RNA that is naturally present in cells or any target RNA *in vitro*.
>
> Page 20, lines 1-3
>
> The invention also provides methods of for specifically cleaving preselected RNA.
>
> Page 12, lines 8-9.
>
> Among other uses, the activity that has now been recognized can now be exploited as an alternative terminating mechanism to RNase H for antisense therapeutics.
>
> Page 17, lines 30-33.
>
> Useful substrates for such dsRNases are also herein provided, as well as affinity matrices comprising such substrates.
>
> Page 13, lines 17-18.
>
> It is clear that alternative terminating mechanisms for degrading target RNA are highly desirable.
>
> Page 18, lines 27-29

To establish a *prima facie* case of lack of specific and substantial utility, the Examiner "must establish that it is **more likely than not that a person of ordinary skill in the art would not consider that <u>any</u> utility asserted by the applicant would be specific and substantial.**" Federal Register 66(4) at 1098 (emphasis added). Applicants submit that any one of the asserted utilities set forth above satisfies the requirement of representing a credible assertion of specific and substantial utility sufficient to satisfy the utility requirement. The above-listed assertions are (a) specific and substantial, and (b) credible from the perspective of the skilled artisan.

I. THE ASSERTED UTILITIES ARE SPECIFIC AND SUBSTANTIAL

The Examiner recognized that, in certain embodiments, the present invention is useful as a substrate for RNase III, but dismissed that utility remarking that there is "no indication from the specification, as filed, that the instantly claimed double stranded RNAs have any utility other than that shared by the entire class of RNase III substrate double stranded RNAs." Office Action at page 2-3. The Examiner appears to require a novel utility, since one could always assert that an invention shares utility with other inventions having the same utility. Certainly, that is not the correct standard. Moreover, the claimed oligonucleotides, in fact, do have specific utilities not shared by the "entire class of RNase III substrates."

The requirement for specific utility is further discussed in the PTO's Revised Interim Utility Guidelines Training Materials (Training Materials):

> Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the inventions.

Training Materials at page 5 (emphasis in original). The Training Materials explain that a general utility is one that is applicable to "the broad class of the inventions." Id. at page 5. As set forth below, it is clear from the specification as filed that the chemically modified oligonucleotides of the present claims have properties, including specificity, stability and affinity, not shared by the broad class of oligonucleotides. In fact, these specific properties disclosed in the specification are not shared by even the substantially narrower class of RNA oligonucleotides, or double-stranded RNA oligoucleotides, or even the narrow class of RNase III substrates. Together and individually, these properties confer upon the claimed compounds specific utilities not shared by all RNase III substrates.

1. Specific Property: Specificity

The claimed compounds have specific and substantial utility as substrates for certain RNases, in preference to certain other nucleases. Certain claimed compounds activate dsRNases (e.g., RNase III), but do not activate, or activate to a lesser extent, RNase H and other nucleases. Such specificity is useful, for example, for characterizing the RNase activities in different cell and tissue types. In certain embodiments, the claimed compounds may be used in assays to identify cells and targets comprising one or more dsRNase. See Page 97, lines 1-2 (noting that "the assays described herein are used to evaluate the presence or absence of the desired dsRNase in a sample.") Despite the Office's contention that the claimed compounds have no utility "other than that shared by the entire class of RNase III substrate double stranded RNAs,"

unmodified dsRNase substrate RNA's are ill suited for such assays, because they also activate other nucleases. Thus, results from assays using unmodified dsRNA's would be impossible to interpret, since any observed RNase activity could be due to dsRNases or could be due to other nucleases. Such assays may be used, for example, to determine the RNase profile for a cell or tissue type or to identify abnormalities in RNase activity in a sample. See e.g., specification at page 14. Specificity for dsRNases relative to other nucleases is not shared by the broad class of oligonucleotides or even the narrow class of RNase III substrates. Rather, the claimed modified oligonucleotides are particularly suited for such use.

2. Specific Property: Stability

Compounds of the present claims are also specifically useful because they are "more stable to exonuclease digestion than an oligoribonucleotide." Specification at page 92 (further noting that "substrates with both phosphorothioate linkages and 2'-methoxy nucleosides was extremely stable.") The specification further teaches that such "features are important because of the abundance of single-strand RNases relative to the double-strand RNase activity in the rat liver and supported the use of non-denaturing assays." Id. Thus, in certain diagnostic and/or therapeutic applications, the claimed compounds are uniquely well suited as substrates due to their stability and nuclease resistance. As discussed above, such utility is not shared by all oligonucleotides or even by all dsRNase substrates.

3. Specific Property: Affinity

Compounds of the present invention further possess specific utilities, which are not shared by all RNase III substrates, attributable to chemical modifications that increase the affinity of one oligonucleotide for the other oligonucleotide of the claimed duplex. Not every RNase substrate is expected to have sufficient affinity to be useful in, for example, *in vitro* or *in vivo* assays, in diagnostics and/or therapeutic settings. In certain such settings, unmodified oligonucleotides will not remain hybridized to the extent necessary to elicit the desired effect, for example the activation of RNase III.

4. Specific Utilities: Diagnostics, Therapeutics and Research

The claimed compounds possess unique properties, as described above, that confer upon them specific utilities. For example, compounds of the present invention can be useful for diagnostic methods as described in the specification:

> The invention further provides diagnostic methods for detecting the presence or absence of abnormal RNA molecules, or abnormal or inappropriate expression of normal RNA molecules in organisms or cells. The invention further provides research reagents for modulating enzyme activity including dsRNase activity in *in vitro* solutions.

Specification at page 14, lines 7-12. Compounds of the broad class of double-stranded RNA molecules are not particularly well suited for such diagnostic use due to their vulnerability to other nucleases; their poor affinity for one another or for a target; and/or their lack of specificity for a particular RNase, such as RNase III. Compounds of the present invention have overcome or reduced these obstacles through chemical modifications as recited in the claims.

While the present invention possesses certain utilities with broad application, for example use as "therapeutics" or "diagnostics" (specification at page 1, lines 20-23), such utilities should not be confused with "general" utilities, as that term is used in the Utility Guidelines and by the Federal Circuit in *In Re Fisher,* 421 F.3d 1365 (Fed. Cir. 2005). *Fisher* involved an attempt to patent express sequence tags (ESTs), which are unique to a specific nucleic acid encoding a specific protein. In *Fisher*, at the time of filing, the identity of that specific protein was unknown and, thus, the utility of that specific protein was also unknown. The Federal Circuit held that because the claimed EST's encoded unknown proteins of unknown function, there was no specific and credible utility. *Id.* at 1376. The present invention differs significantly from *Fisher* because the claimed invention is not sequence dependent and thus, is not limited to a particular nucleic acid or target protein. It is the chemical modifications, not the sequence, that make the claimed oligonucleotides useful.

The specification also describes use of the claimed oligonucleotides as research tools. Indeed, the specification notes that antisense oligonucleotides in general have "proven to be very powerful research tools and diagnostic agents." Specification at page 2, lines 14-15. Since traditional antisense compounds depend on RNase H and because RNase H is not present in every cell and tissue type, such assays could not be run in those cell and tissue types. See, e.g., page 2, lines 32-35. Thus, chemically modified oligonucleotides of the present invention have specific utility as research tools in cells and tissues with little or no RNase H activity. As described above, that utility is not shared by the broad class of dsRNase substrates, since many such substrates lack the affinity, stability and/or specificity to be particularly useful for such applications. As discussed previously, compounds of the invention may also be used to

characterize RNases of different cell and tissue types and/or to identify abnormalities in RNase activity, which may be attributable to a disease.

Because use as a research tool was another utility that the *Fisher Court* rejected, Applicants again address some of the operative differences between the present invention and ESTs. Fisher asserted that ESTs were useful as tools for further research of the ESTs themselves and their corresponding proteins. 421 F.3d at 1376. Thus, the invention was itself the subject further research. *Id.* The court rejected that assertion of utility and distinguished it from a research tool, such as a microscope, which is immediately useful for researching something other than itself (the thing magnified). *Id.* at 1373. Like a microscope, an oligonucleotide of the invention is immediately useful for researching something other than itself. In particular, the claimed chemically modified oligonucleotides are useful, not for further studying the oligonucleotides (as was the case with the Fisher ESTs), but rather for example, for characterizing dsRNase/RNase H profiles of various cells and tissues, as described above, or for reducing the amount of a target protein in a cell. Thus, the claimed compounds are not themselves the object of further testing as warned by the *Fisher Court*. Rather, they are true research tools, useful for studying other molecules and functions in a cell or tissue.

II. THE ASSERTED UTILITIES ARE CREDIBLE

Having asserted that the invention lacks a specific utility, the Examiner did not assess credibility. See Action at page 3. In the interest of advancing prosecution, Applicants will, nevertheless, brifly discuss credibility of the spcecific utilities discussed above.

An assertion of utility is credible unless the logic underlying the assertion is seriously flawed, or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Training Materials at page 5. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. *Id.* A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. *Id.* As detailed herein, the claimed compounds have at least the specific and substantial utility of being substrates for RNase III. The chemical modifications that increase specificity, stability, and affinity of the claimed oligonucleotides make them particularly well suited as RNase III substrates in a variety of applications. A person of ordinary skill in the

art would accept that such compounds are available for the uses disclosed in the specification and summarized herein.

As described above, the specification as filed is replete with credible assertions of specific, substantial and credible utilities. Accordingly, Applicants respectfully submit that the utility requirement of 35 U.S.C. §101 is clearly met by the specification as filed and request reconsideration and removal of the rejection of claims 81, 93, 106, and 176-243 under 35 U.S.C. § 101.

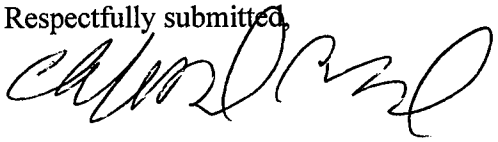
While the above comments address several examples from the specification, Applicants are mindful that, in order to satisfy the utility requirement, an applicant need only provide one credible assertion of specific and substantial utility. Accordingly, Applicants have not addressed every asserted utility and have not addressed well-established utilities at this time. Failure to address well-established utilities in this response should not be interpreted as a lack of any such well-established utilities.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 50-0252 and please credit any excess fees to such deposit account.

Respectfully submitted,



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